UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/112,848	08/27/93	KUCHERLAPATI	R 4364-000-23

EXAMINER: ZISKA, S

ART UNIT	PAPER NUMBER
1804	12

18M2/0329

MORRISON & FOERSTER
2000 PENNSYLVANIA AVENUE, N.W.
WASHINGTON, DC 20006-1812

DATE MAILED: 03/29/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 12/27/95 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire three (3) month(s), 90 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474..
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-12 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-12 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

This application should be reviewed for errors.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-12 are active and examined in this Office Action.

It is noted for the record that the amendments to claims 5, 6, 7 and 9 were not entered since the amendments were incorrectly submitted. Therefore, claims 5, 6, 7 and 9 stand unamended.

The rejection of claims 1-12 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 34-39, 68, 69 and 82 of copending application serial no. 08/031,801 is maintained. Applicants have stated that they prefer to defer submission of any terminal disclaimers pending notification of allowable subject matter. In view of Applicant's arguments, the rejection is maintained.

The rejection of claims 1-12 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 29, 30 and 33-35 of copending application serial no. 07/919,297 is maintained. Applicants have stated that they prefer to defer submission of any terminal disclaimers pending notification of allowable subject matter. In view of Applicant's arguments, the rejection is maintained.

The rejection of claims 1-12 under 35 U.S.C. 112, first paragraph, stands as follows: the rejection directed to the ES cell line is withdrawn in view of the amendments to the claims.

Further, the objection to the claims regarding the term "rodents" and "murine" is withdrawn. The rejection of claims 5-11 requiring the limitation to the J region or kappa constant regions or J and kappa constant region is withdrawn.

The rejection of claim 5 under 35 U.S.C. 112, second paragraph, regarding the phrases "substantially intact" and "and/or" is maintained in view of the non-entry of the amendments to the claims.

The rejection of claims 1-6, 8 and 9 under 35 U.S.C. 103 as being unpatentable over Huxley taken with Hooper and Pachnis is maintained.

The rejection of claims 7, 10 and 11 under 35 U.S.C. 103 as being unpatentable over Hooper taken with Huxley and Pachnis is maintained.

Applicants have argued the rejections simultaneously and therefore their arguments are similarly rebutted. Applicant's arguments, filed December 27, 1994, have been considered but not found to be persuasive. Applicants have argued that at the time the claimed invention was made, the invention was not expected to be successful. Applicants have acknowledged that Pachnis actually suggests substituting ES cells for L cells in the spheroplast fusion method but gives no indication that there would be a reasonable expectation of success. However, contrary to such arguments, Pachnis does infer a reasonable expectation of success

otherwise he would not have suggested the substitution. Neither the author nor one of ordinary skill in the art would suggest substitutions which do not work. Pachnis provides no teaching away from the substitution or provides reasons as to why the substitution would not be expected to work. Applicants have argued that such a substitution would not have been obvious to one of ordinary skill and that those of ordinary skill actually expected failure should spheroplast fusion be applied to ES cells. Applicants have further provided 4 references in support of their position. Applicants have argued that in two of the references, both by Strauss, the authors of the papers used a technique involving lipofection with purified YACs in order to avoid problems associated with spheroplast fusion and Applicants cite Strauss at page 421, right hand column, for support. However, the cited paragraph does not contain a single teaching that there is a problem in the use of spheroplasts per se. Applicant's cited paragraph does not support their arguments. Strauss (Science) used micelles, not spheroplasts, and with a subsequent modification of their initial protocol was able to achieve integration and expression of YACs. There is no mention of the use of spheroplasts or comparison of their method with the spheroplast method. Strauss (EMBO) discloses that the YACs constitute such a small fraction of the DNA available for transfection and "not surprisingly" several investigators found

large portions of the yeast genome present in their stable transfectants. Apparently, the reason that investigators using the spheroplast technique have not been able to achieve transfection of ES cells is that a large amount of the DNA in the spheroplast is the yeast genome and not the YAC of interest. Therefore, the inability to achieve transfection is not related to the technique per se but to the relative ratios of "junk" DNA compared to the desired DNA. Such reasoning is supported by both of the Strauss articles, which showed integration into the ES genome when using purified YACs contained in micelles. There is no evidence in these references that spheroplast fusion would not work. If it is true that most ES cells contained junk DNA (yeast DNA, not the YAC DNA which would contain the gene of interest)after spheroplast fusion, then integration into the ES cell genome is seen to be a reflection of the concentration of YAC DNA and since spheroplasts contain mostly junk DNA, the number of transfectants screened would have to be larger than the number screened if there were less junk DNA. Since identification of the clone containing the YAC DNA is relatively straight forward using techniques already available in the prior art as well as the submitted art, the references do not teach away from using the spheroplast technique. Strauss and Strauss are useful for pointing out that once the YAC is purified away from the junk DNA, which is to say that once the concentration of desired YAC

DNA is increased compared to the concentration of the yeast DNA, ES cells are readily transformed. Thus in the spheroplast method, at least one ES cell would contain the YAC DNA and would not be subject to the postulated "mutagenic influences" postulated to exist by Strauss and relied upon by applicants as evidence of lack of reasonable expectation of success.

Applicants have next discussed the third reference, Pavan, and argued that while describing the successful modification of carcinoma cell lines using spheroplast fusion, the Pavan article specifically states that this technology is not directly translatable into corresponding technology for modifying ES cells and point to the PEG fusion techniques which allegedly need to be "developed". However, contrary to such arguments, a detailed reading of the statements of Pavan:

"The successful use of this procedure to generate transgenic mice would require development of PEG fusion techniques in which ES cells retain the ability to colonize the germ line of the chimera, an ability which is readily lost during manipulations of these cells"

indicates that the ability to colonize the germ line is an ability which is lost during manipulations of the cells independent of whether or not PEG is present. ES cells are known in the art to lose the ability to colonize the germ line no matter what transfection technique is applied.

Applicants have argued that the fourth reference, Bradley, teaches that it was only "potentially" that YAC vectors could be

transferred to ES cells and that the state of the art in 1992 presented no reasonable expectation of success. However, contrary to such arguments, Bradley does not provide evidence as to why YACs would not be expected to work and "potentially" is not the equivalent of "would not be expected".

Applicants have argued that while Pachnis may have suggested substituting ES cells for the L cells in the spheroplast fusion method, Pachnis provides no basis for the expectation of success and that evidently Pachnis was unaware of the reservations of others in the field. However, contrary to such arguments, Pachnis does infer a reasonable expectation of success otherwise he would not have suggested the substitution. Neither the author nor one of ordinary skill in the art would suggest substitutions which do not work. Pachnis provides no teaching away from the substitution or provide reasons as to why the substitution would not be expected to work. Applicants' assertions that "Pachnis seemed to be unaware of the reservations of others in the field" are speculation; clearly even if Pachnis did know of the reservations of others, he did not address the issue.

Applicant's addition of claim 12, encompassing a new limitation, has necessitated a new ground of rejection and this Office Action will be made Final. Note that claim 5 did not require the limitation of immunoglobulin DNA.

Claim 12 is rejected under 35 U.S.C. § 103 as being unpatentable over Huxley, Hooper and Pachnis as applied to claims 1-6, 8 and 9 above, and further in view of Traver et al., Shimizu et al. and Berman et al. Claims 1-6, 8 and 9 were rejected for reasons as stated above. Traver discloses that the ability to transfer large pieces of DNA enables the study of the effects of cis-acting regulatory elements operating at great distance or mechanisms such as alternative splicing. Shimizu discloses transgenes containing rearranged human $V_HDJ_{H-}C_{mu}$ genes. Berman discloses the gene locus of the human immunoglobulin heavy chain and further discloses the nucleotide sequence of 21 novel human Vh genes (Abstract). Therefore, Shimizu and Berman taken together teach that constructs containing human immunoglobulin genes were known in the art at the time the claimed invention was made. It would have been obvious to one of ordinary skill to modify the YAC DNA of Huxley by substituting DNA encoding human immunoglobulin genes in order to modify the genome of a mammalian cell to express human immunoglobulin genes in view of the teachings of Pachnis, teaching that "The application of the YAC transfer system to pluripotent embryonic stem cells which are capable of colonizing the somatic as well as the germ cell lineages when implanted into early mouse embryos, could lead to the generation of transgenic animals that carry and transmit any YAC". One of ordinary skill, desiring to study human

immunoglobulin genes would have been motivated to use YACs as a method of DNA transfer since Berman discloses that the immunoglobulin gene locus is very large and Traver discloses the desirability and practicality of transferring large pieces of DNA.

Accordingly, the modification of the method of the Huxley, Pachnis and Hooper by substituting DNA encoding the immunoglobulin genes as suggested by Traver, Berman and Shimizu in order to obtain a method wherein said xenogeneic DNA comprises a portion of an immunoglobulin locus was within the ordinary skill in the art at the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is prima facie obvious, as evidenced by the references, especially in the absence of evidence to the contrary.

No claim is allowed.

Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION

IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO FAX center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (30 November 15, 1989). The CM1 Fax Center number is (703) 308-4227.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Suzanne Ziska, Ph.D., whose telephone number is (703)308-1217.

SUZANNE E. ZISKA
PRIMARY EXAMINER
GROUP 1800